

### REMARKS

Applicants have carefully studied the Final Office Action mailed on October 6, 2004, which issued in connection with the above-identified application. Applicants gratefully acknowledge that claims 56, 57, 60, 61, and 62 have been allowed. The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the remaining claims in condition for allowance. Favorable reconsideration and allowance of all of the present claims are respectfully requested.

### **Pending Claims**

Claims 11, 12, 16, 29, 51, and 56-63 were pending and at issue in the application. Claims 56, 57, 60, 61, and 62 have been allowed. Claims 51, 63, 11, 12, and 16 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Claims 29 and 58 (and 59?) have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 29 and 58 have been also rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement and under 35 U.S.C. §102(b) as being anticipated by Boehringer Mannheim random hexamer mixtures (1997 Catalog No. 1 277 081).

Claims 11, 12, 16, 51, and 63 have been canceled without prejudice or disclaimer. Applicants note for the record that these claims have been canceled solely to expedite prosecution and not as an admission of lack of patentability of the canceled claims. Applicants reserve the right to pursue canceled subject matter in a continuing application.

To expedite prosecution, claims 29 and 58 have been amended by deleting the recitation “CASP8 gene-specific” and adding the recitation of the oligonucleotide primer length of “at least

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<sup>1</sup> Applicants respectfully note that, based on the Examiner’s statements in different parts of Section 11 (pages 5-6 of the Office Action), it is not clear whether claim 59 is also rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

10 nucleotides". The oligonucleotide primer length limitation is supported, for example, by the definition of the term "oligonucleotide" provided at page 17, lines 23-26 of the specification.

Allowed claims 56 and 57 have been amended to correct minor typographical errors.

New claims 66-71 have been added to more particularly point out and distinctly claim the invention. Specifically, new independent claim 66 and its dependent claims 67 and 68 have been added following the implied Examiner's suggestion provided in Section 9 (page 3) and the first full paragraph at page 4 of the Office Action. New independent claim 69 and its dependent claims 70 and 71 have been added following the Examiner's suggestion provided in the last sentence of the paragraph bridging pages 4 and 5 of the Office Action. Claim 69 recites the term "aggressive neuroblastoma", which is disclosed at page 28, line 19 of the present specification. New claims 66-71 find support, *e.g.*, in the original claims 10-12 and 15-16 and at page 3, lines 4-9, page 7, lines 11-23, page 28, line 15 - page 29, line 7, and Examples 2-4 of the present specification.

No new subject matter has been added as a result of these amendments, no new search is required, and no new issues are raised. Upon entry of the above-identified amendments, claims 29, 56-62 and 66-71 will be pending.

### **35 U.S.C. §112, First Paragraph Rejections**

In the Action (Section 9), the Examiner has maintained the rejection of claims 51, 63, 11, 12, and 16 under 35 U.S.C. §112, first paragraph, for lack of enablement. Specifically, the Examiner contends that the specification, while being enabling for (i) methods of prognosis of neuroblastoma comprising the detection of methylation of *CASP8* gene<sup>2</sup> and (ii) methods of differentially diagnosing high-risk neuroblastoma from low-risk neuroblastoma comprising the

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<sup>2</sup> See Section 9 (page 3) and the first full paragraph at page 4 of the Office Action.

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detection of methylation of *CASP8* gene<sup>3</sup>, does not reasonably provide enablement for methods of diagnosis or prognosis of cancers other than neuroblastoma.

As claims 51, 63, 11, 12, and 16 have been canceled, the rejection of these claims is rendered moot. As stated above, claims 51, 63, 11, 12, and 16 have been canceled solely to expedite prosecution and not as an admission of lack of enablement of diagnosis or prognosis of cancers other than neuroblastoma. Applicants reserve the right to pursue this subject matter in a continuing application.

As noted above and following the implied Examiner's suggestions provided in the Office Action, new claims 66-71 directed to the methods of diagnosis or prognosis of neuroblastoma comprising the detection of methylation of *CASP8* gene have been added.

In light of the above-presented amendments and arguments, the rejections under 35 U.S.C. §112, first paragraph, are believed to be overcome and withdrawal of such is kindly requested.

### **35 U.S.C. §102 and §112 Rejections of Claims 29, 58 and 59**

In the Office Action (Section 10), the Examiner has maintained the rejection of claims 29 and 58 under 35 U.S.C. §102(b) as being anticipated by Boehringer Mannheim random hexamer mixtures (1997 Catalog No. 1 277 081). The Examiner contends that claims 29 and 58 read on random hexamer mixtures, because the primers are to be used for the amplification of at least a part of the 5' untranslated region or for the amplification of sequences that comprise either SEQ ID NO: 1 or SEQ ID NO: 2. The Examiner also states that the term "CASP8 gene-specific oligonucleotide" introduced in the previous amendment does not obviate the rejection, because, allegedly, the term "CASP8 gene-specific" is indefinite and is not disclosed in the specification.

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<sup>3</sup> See the last sentence of the paragraph bridging pages 4 and 5 of the Office Action.

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Because of this term, the Examiner has also rejected claims 29 and 58 (and 59<sup>4</sup>) under 35 U.S.C. §112, second paragraph, as being indefinite (Section 11 of the Office Action) and under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement (Section 12 of the Office Action).

Although applicants respectfully disagree with the Examiner's rejections and note that (i) methylation PCR relies on the use of sequence-specific PCR primers and not random hexamers sold by Boehringer Mannheim, which do not allow the sequence-specific amplification of at least a part of the 5' untranslated region or sequences that comprise either SEQ ID NO: 1 or SEQ ID NO: 2<sup>5</sup> and (ii) the term "*CASP8* gene-specific" is used within its standard meaning in the art and does not need to be defined, in order to expedite prosecution, the term "*CASP8* gene-specific" has been deleted in claims 29 and 58, and claim 29 has been further amended to recite the oligonucleotide primer length limitation of "at least 10 nucleotides". This oligonucleotide primer length limitation is supported by the definition of the term "oligonucleotide" provided at page 17, lines 23-26 of the specification. Claims 29, 58 and 59 as amended recite the primers that are at least 10 nucleotides long. Accordingly, these claims do not encompass any oligonucleotides that are shorter than 10 nucleotides such as random hexamer mixtures sold by Boehringer Mannheim.

In light of the above-presented amendments and arguments, the rejections of claims 29, 58 and 59 are believed to be overcome and withdrawal of such is kindly requested.

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<sup>4</sup> Applicants respectfully note that, based on the Examiner's statements in different parts of Section 11 (pages 5-6 of the Office Action), it is not clear whether claim 59 is also rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

<sup>5</sup> See the arguments presented in response to the previous Office Action dated 04/06/04.

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**CONCLUSION**

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that, in addition to allowed claims 56, 57, 60-62, claims 29, 58, 59, and 66-71 are now also in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,



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